

A Petition to Accept Photographs and Formal Drawings

Applicant hereby petitions under 37 CFR 1.84(b), that acceptance of the accompanying photographs be submitted, specifically Figs. 9 and 15 as formal drawings to be made of record in the above identified case. Figs. 1-8, and 10-14 are also submitted as formal drawings.

REMARKS

The Invention

Applicants' claims are directed to a fluorogenic peptide, and methods of preparing and using the peptide. A unique feature of the Applicants' invention is the attachment of the peptide to a solid support *through the fluorogenic moiety*. As explained below, this element is neither disclosed nor suggested by the art of record.

Status of the Claims

Claims 1-112 are pending in the present application. Claims 1-83 were substantively examined. New claims 84-112 are added and their examination on the merits is respectfully requested. Claims 7, 18-20, 36 and 37 are amended by substituting the article "The" for "A" at the beginning of the claim.

Claims 1, 16 and 32 are amended to include $\text{NR}^{18}\text{R}^{19}$ in the Markush group for $\text{R}^1\text{-R}^6$. The substituents R^{18} and R^{19} are also inserted into the Markush group for $\text{R}^7\text{-R}^{13}$. The amendment to the claims is supported in the specification as filed. For example, claim 73 recites $\text{NR}^{18}\text{R}^{19}$ in the Markush group for $\text{R}^1\text{-R}^6$ and the identities of R^{18} and R^{19} in claim 73 are identical to those recited for these substituents in claims 1, 16 and 32. Claim 16 is further amended to recite that the substituent Y is an organic functional group. Claim 32 is further amended to remove the redundant recitation of selected members of the genus "organic functional group." No new matter is added by any of the amendments to the claims.

Claims 17, 20, 33-34, 37-39, 42 and 55-59 are objected to as being dependent on a rejected base claim. The Examiner has indicated that the claims objected to would be allowable if rewritten in appropriate form. Accordingly, Applicants submit new claims 84-113, which are the claims objected to rewritten as suggested by the Examiner. Applicants request an indication of the allowability of new claims 84-113.

Claims 73-76 and 78-83 are deemed allowable over the art of record. The Applicants thank the Examiner for the indication of the allowability of these claims.

Claims 60, 72 and 77 are rejected under 35 U.S.C. §112, second paragraph as being allegedly indefinite. Applicants respond by amending claims 72 and 77 to correct the typographical errors that prompted the rejections. Claim 72 is amended by changing step (c)

to step (d). Claim 77 is amended to depend from claim 76. Claim 60 is explained and its clarity is asserted.

Claims 1-16, 18-19, 21-32, 35-36, 40-41, 43-54 and 60-72 are rejected under 35 U.S.C. §102(b) as being anticipated by or, alternatively, under 35 U.S.C. §103(a) as being obvious over the disclosure of Del Neary et al. ("Del Neary"). Applicants respond with a combination of amendment and traverse.

Response to Claim Rejections Under 35 U.S.C. §112

Claims 60, 72, and 77 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 60 is rejected because of its use of the term "located." The Action states that it is unclear whether "located" refers to a physical location or a peptide region. Claim 60 recites that the "said first peptide is *located* at a first region of a substrate" and that "said second peptide is *located* at a second region of a substrate." Thus, claim 60 unambiguously refers to regions of a substrate, not regions of a peptide.

Claim 72 is rejected because it presents a claim with two (c) steps. The typographical error in claim 72 is remedied by replacing "(c)" with "(d)" in amended claim 72.

Claim 77 is rejected for being dependent on claim 78. The typographical error is remedied by replacing "78" with "76" in amended claim 77. Claim 76 refers to "an active ester of a carboxylic acid". Claim 77 states that "said active ester is the nitrotriazole ester of acetic acid". Thus, it is apparent that claim 77 appropriately depends from claim 76.

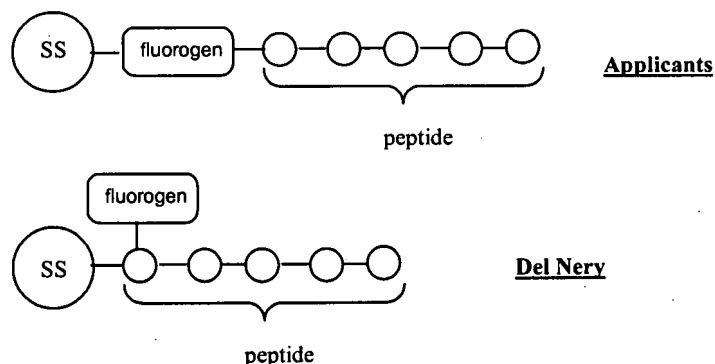
As each of the rejections under 35 U.S.C. §112, second paragraph is overcome by explanation or amendment, Applicants respectfully request the withdrawal of the rejections under 35 U.S.C. §112, second paragraph.

Response to Claim Rejections Under 35 U.S.C. §§ 102(b) and 103(a)

Claims 1-16, 18-19, 21-32, 35-36, 40-41, 43-54, and 60-72 are rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious

over Del Nery, *et al.* (*Biochem. J.*, **323**:427-433 (1997)). Applicants respectfully submit that Del Nery neither discloses nor suggests a fluorogenic peptide attached to a solid support through the fluorogenic moiety such as claimed by the Applicants. Moreover, Del Nery neither discloses nor suggests peptides that include the coumarin components of Applicants' peptides set forth in the amended claims.

The structures of the solid-phase libraries of the Applicants and Del Nery are compared in the figure below.



In the Applicants' library, the peptide is linked to the solid support (SS) through the fluorogenic moiety. In contrast, the Del Nery peptides are bound to the solid support through the C-terminal amino acid residue. The fluorogen is a substituent on a side chain of the amino acid and is not directly attached to the solid support. The structure of the Del Nery peptides is discussed in greater detail below.

Del Nery discloses a PEGA-resin-bound peptide library. The peptides have the structure $Y(NO_2)X^1X^2X^3X^4(K/R)X^5X^6K-(Abz)-PEGA1900$ (428, column 1, directly beneath "Synthesis of a substrate library for cruzipán"). Del Nery's resin-bound peptide library does not include a coumarin fluorogenic moiety. Moreover, the resin-bound peptides are not bound to the resin through a fluorogenic moiety. The Abz moiety is attached to an amine side chain of lysine not to both the peptide and the solid support. The position of the Abz moiety on the lysine side chain amine is indicated by the use of "(Abz)" in the peptide formula and confirmed by the synthetic scheme used to prepare the compound:

the resin was coupled with FMOC-Lys(Boc)-Opfp and then washed with...TFA... Boc-Abz-Odhbt...were added in DMF...

Thus, the lysine is coupled directly to the resin, the Boc protecting group on the ϵ -amine of the lysine is cleaved and the deprotected amine is reacted with the active ester of Boc-protected Abz.

Del Nery also discloses a solution phase peptide library ("Substrates") in which the peptides include MCA (methyl coumarin amide):

peptidyl-MCA substrates were synthesized by the standard solution-phase peptide synthesis procedure starting from protected aminoacyl-MCA...

Peptides prepared by "standard solution-phase" synthetic methods are not immobilized on a solid support. Thus, although Del Nery discloses peptides that are derivatized with MCA, Del Nery does not teach a peptide immobilized on a solid support through a fluorogenic coumarin linker moiety.

Applicants' claims 1, 32, and 86 and their dependents are directed to a composition in which a fluorogenic moiety is directly attached to a solid support and the peptide is attached to the solid support through the fluorogenic moiety. A bond between the fluorogenic moiety and the solid support is required by the claims:

...with the proviso that at least one of R^1 , R^2 , R^3 , R^4 , R^5 and R^6 is $-R^{14}$ -SS...SS is a solid support.

The fluorogenic moiety is derivatized with a peptide or with a functional group that provides a starting group for peptide synthesis on the solid supported fluorophore. As Del Nery neither discloses nor suggests a peptide that is attached to a solid support through a fluorogenic moiety, claims 1, 32, and 86 and their dependents are neither anticipated nor rendered obvious by the Del Nery reference. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 1 and 32 and their dependents under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Del Nery and an indication of the allowability of claim 86 and its dependents.

Claims 16-31, 84 and 85 are directed to a peptide that includes a coumarin moiety attached at its C-terminus and methods of using the peptide in various assays. As discussed above, Del Nery discloses peptides that include methylcoumarin amide. As

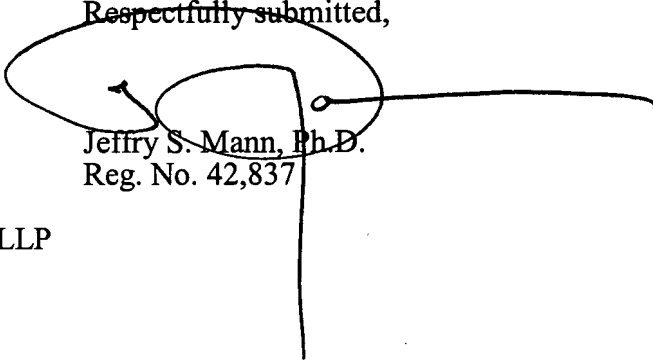
amended, Applicants' claims do not encompass peptides that include methylcoumarin amide (i.e., Y is not methyl). Accordingly, Applicants respectfully request notification of the allowability of claims 17, 20, 84 and 85 and withdrawal of the rejections of claims 16, 18-19, and 21-31 under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Del Neary.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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